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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/733,387	12/07/2000	Gregory Donoho	LEX-0104-USA	7426

24231 7590 11/26/2003

LEXICON GENETICS INCORPORATED
8800 TECHNOLOGY FOREST PLACE
THE WOODLANDS, TX 77381-1160

EXAMINER	
LI, RUIXIANG	

ART UNIT	PAPER NUMBER
1646	

DATE MAILED: 11/26/2003

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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Paper No. 1103

Application Number: 09/733,387
Filing Date: December 7, 2000
Appellant(s): DONOHO ET AL.

David W. Hibler
For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed on 23 July 2003.

(1) Real Party in Interest

A statement identifying the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

A statement identifying the related appeals and interferences which will directly affect or be directly affected by or have a bearing on the decision in the pending appeal is contained in the brief.

(3) Status of Claims

The statement of the status of the claims contained in the brief is correct.

(4) Status of Amendments After Final

The appellant's statement of the status of amendments after final rejection contained in the brief is correct.

(5) Summary of Invention

The summary of invention contained in the brief is essentially correct, except the asserted utilities for the claimed invention are currently being disputed.

(6) Issues

The appellant's statement of the issues 1 and 2 in the brief is correct. Regarding issues 3 and 4, claims 1, 6, and 9 are properly rejected under 35 U.S.C. §112, first paragraph for scope enablement (if the nucleic acid molecule of SEQ ID NO: 43 or encoding the amino acid sequence of SEQ ID NO: 44 were to have a patentable utility) and written description. Claims 7 and 8 are not rejected.

(7) Grouping of Claims

Appellant's brief includes a statement that the claims stand or fall together.

(8) Claims Appealed

The copy of the appealed claims contained in the Appendix to the brief is correct.

(9) Prior Art of Record

Ji et al., G-protein-coupled receptors, J. Biol. Chem. 273:17299-17302, 1998.

Peer Bork and Eugene V. Koonin, Predicting functions from protein sequences--where are the bottlenecks? Nature Genetics 18:313-318,1998.

Yan et al., Two-amino acid molecular switch in an epithelial morphogen that regulates binding to two distinct receptors. 290: 523-527, 2000.

(10) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

Claim Rejections—35 U.S.C. § 101

Claims 1-3 and 6-9 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a specific and substantial asserted utility or a well-established utility.

Claims 1-3 and 6-9 are drawn to the nucleic acid molecule of SEQ ID NO: 43 that encodes a human protein that shares sequence similarity with mammalian membrane proteins, G-protein coupled receptors (GPCRs). The claimed invention is not supported by either a specific and substantial asserted utility or a well-established utility. A specific and substantial utility is one that is particular to the subject matter claimed and that identifies a "real world" context of use for the claimed invention which does not require further research.

The specification asserts that the nucleic acid sequences of the present invention encode human GPCRs because the proteins encoded by the present nucleic acid sequences have structural motifs found in the GPCRs family (see, e.g., Summary of the Inventiona at page 2). The specification discloses that the nucleic acid sequences of the present invention can be detected in human spleen, bone marrow, and adipose, cells (page 2, lines 13-14). However, there is no disclosure of the ligand(s), biological functions, or any physiological significance of the putative GPCRs; there is no disclosure of any evidence indicating that the putative GPCRs are truly functional GPCRs and are involved in signal transduction pathway involving G-proteins or PPG proteins as being asserted; there is no disclosure of any evidence indicating that the claimed nucleic acid sequences are expressed at altered levels or forms in any specific, diseased tissue, as compared with the healthy control tissue. Thus, the claimed nucleic acid molecules lack a specific and substantial utility.

Appellant asserts a number of utilities for the claimed nucleic acid molecules apparently based upon the sequence homology of the proteins encoded by the claimed nucleic acid molecules to GPCRs: the encoded proteins have structural motifs found in the GPCR family. Nonetheless, the specification fails to disclose the degree of homology of the putative GPCRs with any particular functional GPCRs. The specification even fails to identify the specific seven transmembrane domains—where each domain is located. The state of the art in protein science indicates that it is impossible to predict precisely protein functions solely based upon sequence homology. In view of the diversity of structure and functions of the proteins, prediction of function

using comparative sequence analysis may lead to the creation and propagation of assignment errors if not performed appropriately (Peer Bork and Eugene V. Koonin, Predicting functions from protein sequences–where are the bottlenecks? *Nature Genetics* 18:313-318,1998). There are putative seven transmembrane molecules, which do not appear to be coupled to a G protein (Ji et al., G-protein-coupled receptors, *J. Biol. Chem.* 273:17299-17302, 1998). In certain cases, a change of two-amino acid residues in a protein results in switching the binding of the protein from one receptor to another (Yan et al., Two-amino acid molecular switch in an epithelial morphogen that regulates binding to two distinct receptors. *Science* 290: 523-527, 2000). Thus, the asserted utilities in the specification based upon the protein sequence homology are not specific and substantial.

The specification asserts that the claimed nucleic acid sequences can be used to regulate gene expression (page 5, 3rd paragraph; page 9, 2nd paragraph). The specification also asserts utilities of the claimed nucleic acid molecules as hybridization probes for screening libraries (page 11, 1st paragraph), in determining the genomic structure (page 11), and in gene chip (page 33). The specification further asserts the use of the claimed protein in generation of antibodies (page 15, line 1). However, such uses are all considered research uses only designed to identify a particular function of the claimed molecules and are not a substantial utility. See, e.g., *Brenner v. Manson*, 383 U.S. 519, 148 USPQ 689 (Sup. Ct. 1966) wherein a research utility was not considered a "substantial utility." Moreover, such uses are not specific to the instant molecule, rather applicable to any nucleic acid molecules or proteins.

The specification further asserts that the claimed nucleic acid molecules can be used to identify mutations associated with a particular disease or in diagnostic/prognostic assays (page 5, last paragraph). The specification also asserts that the molecules of the present invention, nucleic acid molecules, proteins, fusion proteins, and antibodies "can be useful" for the treatment of diseases, or for screening agonists, antagonist, and drugs (page 3, last paragraph; page 4, last paragraph-page 5, 1st paragraph). These asserted utilities are not specific and substantial because they do not identify or reasonably confirm a "real world" context of use. The specification does not disclose any diseases or conditions that are associated with or can be treated with the claimed molecules. Clearly, further research would be required to identify a disease that is associated with the claimed molecules or a disease that can be treated with the claimed molecules. See *Brenner v. Manson*, 383 U.S. 519, 148 USPQ 689 (Sup. Ct. 1966), noting that "a patent is not a hunting license. It is not a reward for the search, but compensation for its successful conclusion."

The invention also lacks a well-established utility. A well established utility is a specific, substantial, and creditable utility that is well known, immediately apparent, or implied by the specification's disclosure of the properties of a material. The assertion that the proteins encoded by the claimed nucleic acid molecules have sequence homology to GPCRs does not endow the claimed molecules with a specific and substantial utility. No art of record discloses or suggests any property or activity for the claimed molecules such that another non-asserted utility would be well established for the claimed invention.

In summary, all the asserted uses of the claimed invention are simply starting points for further research and investigation into potential practical uses of the claimed nucleic acids. "Congress intended that no patent be granted on a chemical compound whose sole 'utility' consists of its potential role as an object of use-testing." *Brenner v. Manson*, 148 USPQ at 696.

Claim Rejections—35 U.S.C. § 112, First Paragraph (Enablement)

Claims 1-3 and 6-9 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

Furthermore, even if the nucleic acid molecule of SEQ ID NO: 43 or encoding the amino acid sequence set forth in SEQ ID NO: 44 were to have a patentable utility, the instant disclosure would not be found to be enabling for the full scope of the claimed invention comprising a genus of at least 22 contiguous nucleotides of SEQ ID NO: 43.

The factors that are considered when determining whether a disclosure satisfies enablement requirement include: (i) the quantity of experimentation necessary; (ii) the amount of direction or guidance presented; (iii) the existence of working examples; (iv) the nature of the invention; (v) the state of the prior art; (vi) the relative skill of those in the art; (vii) the predictability or unpredictability of the art; and (viii) the breadth of the claims. *Ex Parte Forman*, 230 USPQ 546 (Bd Pat. App. & Int. 1986); *In re Wands*, 858 F. 2d 731, 8 USPQ 2d 1400 (Fed. Cir. 1988).

Claim 1 recites a genus of nucleic acid molecules of any size that has at least 22

contiguous nucleotides of SEQ ID NO: 43. However, other than the nucleic acid molecule of SEQ ID NO: 43 or the nucleic acid molecule encoding the amino acid sequence set forth in SEQ ID NO: 44, the specification has not provided sufficient guidance and information regarding the structural and functional requirements commensurate in scope with what is encompassed by the instant claim. The specification fails to show (i) which portions of SEQ ID NO: 43 are critical to the activity of the protein of SEQ ID NO: 44; and (ii) what modifications (e.g., substitutions, deletions or additions) one can make to SEQ ID NO: 43 will result in protein mutants with the same functions as the protein of SEQ ID NO: 44. The state of the art (See, e.g., Ngo, et al, *The Protein Folding Problem and Tertiary Structure Prediction*, 1994, Merz, et al. (ed.), Birkhauser, Boston, MA, pp. 433 and 492-495) is such that the relationship between sequence of a protein and its activity is not well understood and is not predictable. Excising out portions of a protein or modifications to a protein, e.g., by substitutions or deletions, would often result in deleterious effects to the overall activity and effectiveness of the protein.

Accordingly, the disclosure fails to enable such a myriad of the claimed nucleic acid molecules that not only vary substantially in length but also in nucleotide composition and to provide any guidance to those skilled generally on how to make and use the claimed genus of nucleic acid molecules. Thus, it would require undue experimentation for one skilled in the art to make and use the claimed genus of nucleic acid molecules embraced by the instant claim.

Claim Rejections—35 U.S.C. § 112, First Paragraph (Written Description)

Claim 1 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention.

The specification discloses a nucleotide sequence set forth in SEQ ID NO: 43 or encoding the amino acid sequence set forth in SEQ ID NO: 44. However, Claim 1 recites a genus of nucleic acid molecules comprising at least 22 contiguous nucleotides of SEQ ID NO: 43. Thus, it encompasses virtually any random sequence of any length as long as it has a stretch of at least 22 consecutive nucleotides that is the same as SEQ ID NO: 43.

The instant disclosure of a single species of nucleic acid of SEQ ID NO: 43 does not adequately support the scope of the claimed genus, which encompasses a substantial variety of subgenera including full-length genes. A description of a genus of cDNA may be achieved by means of a recitation of a representative number of cDNAs, defined by nucleotide sequence, falling within the scope of the genus, or of a recitation of structural features common to the genus, which features constitute a substantial portion of the genus. *Regents of the University of California v. Eli Lilly & Co.*, 119 F3d 1559, 1569, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997). The instant disclosure fails to provide sufficient description information, such as definitive structural or functional features of the claimed genus of nucleic acid molecules. There is no description of the conserved regions that are critical to the structure and function of the genus claimed.

There is no description of the sites at which variability may be tolerated and there is no information regarding the relation of structure to function. Furthermore, the prior art does not provide compensatory structural or correlative teachings to enable one skilled in the art to identify the encompassed nucleic acid molecules as being identical to those instantly claimed.

Due to the breadth of the claim genus and lack of the definitive structural or functional features of the claimed genus, one skilled in the art would not recognize from the disclosure that the applicant was in possession of the claimed genus.

(11) Response to Argument

A. Do claims 1-3 and 6-9 lack a Patentable Utility?

Beginning at page 4 of the Brief, Appellant argues that the amino acid sequence encoded by the claimed nucleotide sequence shares up to 100% homology with sequences present in GenBank which have been annotated as G-protein coupled receptor, in particular GPR97 (Exhibits A-E). Thus, it is sufficient to justify that the protein encoded by the claimed nucleic acid is a GPCR and meet the requirements of 35 U.S.C. § 101.

Appellant's arguments have been fully considered but are not deemed to be persuasive for the following reasons. First, the key issue at dispute is not a matter of whether the present nucleic acids encode GPCRs; rather, it is a matter of whether the present nucleic acids encode GPCRs with defined biological functions; it is a matter of whether the present nucleic acid sequences have a patentable utility. The annotations

for the published sequence in Genbank are based upon sequence homology and there is no sufficient information which defines unambigously the functions of the published sequences.

Secondly, the art teaches that it is impossible to predict precisely the functions of protein molecules solely base upon sequence analysis, in view of the diversity of structure and functions of GPCRs (Bork and Eugene V. Koonin, *Nature Genetics* 18:313-318,1998). There were nearly 2000 GPCRs up to 1998 and they are classified into over 100 subfamilies according to sequence homology, ligand structure, and receptor function. There are putative seven transmembrane molecules, which do not appear to be coupled to a G protein (Ji et al., *J. Biol. Chem.* 273:17299-17302, 1998; see beginning of the article). A variety of studies have shown that minor differences in sequence can account for different binding affinities and activities. For example, a change of two-amino acid residues in a protein results in switching the binding of the protein from one receptor to another (Yan et al., *Science* 290: 523-527, 2000).

Furthermore, there is no single well-established utility for the GPCR family due to the great diversity in structures and functions of the GPCR family. Even for a subfamily of the GPCR, the structure and biological activities may vary broadly. The functions of a GPCR has to be determined experimentally. Therefore, even the sequence analysis can place a GPCR into the GPCR family; such an assignment does not render a specific biological function and thus a well-established utility to the GPCR, as is the case here.

Finally, it is noted that the instant application was filed December 7, 2000. No evidence has been brought forth during the prosecution history regarding the specific

biological functions or physiological significance of the proteins encoded by the claimed nucleic acid sequences. It clearly weighs in favorite of the Examiner's position that the functions of the proteins encoded by the claimed nucleic acid sequences remain elusive.

At the bottom of page 5 of the Brief, Appellant argues that the amino acid sequence encoded by the claimed nucleotide sequence shares 68% percent identity and 78% similarity at the amino acid level with a sequence present in GenBank which has been annotated as "Mus musculus Pb99 gene sequence" (GenBank, Accesion No. AF249738, Exhibit F). The protein encoded by the gene sequence has been functionally characterized as a G-protein coupled receptor (Mol. Cell. Biol. 20:4405-4410, 2000, Exhibit G).

This has been fully considered but is not deemed to be persuasive because (i) the annotation for the published sequence in Genbank is, again, based upon sequence homology and there is no sufficient and credible information that indicates the published sequence is a truly functional GPCR; (ii) careful evaluation of the publication by Sleckman et al. (Mol. Cell. Biol. 20:4405-4410, 2000) leads to the conclusion that this paper asserts that the cDNA encodes a putative protein that has seven hydrophobic domains similar to those of G-protein coupled receptors (see Abstract). Once again, this prediction was based upon sequence homology without sufficient evidence indicating that the protein is functional GPCR; and (iii) even if the cDNA of Sleckman et al. encodes a functional GPCR, the sequence similarity does not render the sequence of

the present invention a specific function and a patentable utility because there is no single well-established utility for the GPCR family due to the great diversity in structures and functions of the GPCR family and the functions of a GPCR has to be determined experimentally as noted immediately above.

Beginning at the second paragraph of page 6 of the Brief, Appellant criticizes the rejection's use of Bork and Koonin (Nature Genetics 18:313-318,1998), Ji et al. (J. Biol. Chem. 273:17299-17302, 1998), and Yan et al. (Science 290:523-527, 2000). Appellant argues that these articles fail to support the lack of utility of the presently claimed sequences.

Appellant urges that the Bork and Koonin article is hardly indicative of a high level of uncertainty in assigning function based on sequence. This has been fully considered but is not deemed to be persuasive because it ignores the overall teachings of Bork and Koonin article. Bork and Koonin's remarks clearly indicate that the potential importance of sequence analysis in extracting functional signal. However, Bork and Koonin do not teach, in any means, that sequence analysis alone can define the biological functions. In fact, Bork and Koonin clearly teach that the exponential growth of sequence data does not necessarily lead to an increase in knowledge about the functions of genes and their products and that prediction of function using comparative sequence analysis may lead to the creation and propagation of assignment errors if not performed appropriately (Abstract). Bork and Koonin further teach that many proteins are multifunctional, assignment of a single function, which is still common in genome

progects, results in loss of information and outright errors (Table 2). While sequence analysis is important, the information provided or "predicted" based upon sequence homology can only be used as guidance in determining functions or activities of a molecule by experiments. Any functions predicted based upon the sequence homology will have to be confirmed ultimately by direct experimentation.

Appellant urges that an exact quote from Ji et al. completely undermines the question of asserted utility based upon protein homology: "a substantial degree of amino acid homology is found between members of a particular subfamily, but comparisons between subfamilies show significantly less or no similarity". Appellant further urges that homology with members of a G-protein coupled receptor is indicative that the particular sequence is in fact a member of that subfamily. This has been fully considered but is not deemed to be persuasive for the following reasons. First, the Examiner notes that the critical issue at dispute is not a matter of whether the present nucleic acids encode GPCRs; rather, it is a matter of whether the GPCRs encoded by present nucleic acids have defined biological functions and have a patentable utility. The cited statement simply indicates that a substancial degree of amino acid homology is found among members of a particular subfamily. However, two sequences sharing certain degree homology do not necessarily have the same functions. Secondly, the specification merely asserts that the nucleic acid sequences of the present invention encode putative human G-protein coupled receptors (see, e.g., Summary of the Invention). Nowhere in the specification specifies a functional G-protein coupled receptor or a subfamily of G-protein coupled receptors with which the proteins encoded

by the present nucleic acid sequences share sequence homology and the degree of homology. Finally, Ji et al. clearly teach there are putative seven transmembrane molecules, which do not appear to be coupled to a G protein (page 17299, third paragraph of left column, Ji et al.). Even if the proteins encoded by the present nucleic acid sequences were able to be placed, based upon sequence homology, in the GPCR family, there would still not a patentable utility for the claimed invention because there is no common use and thus there is no well established utility for the diversified GPCR family. In this regard, it is noted that there are nearly 2000 G-protein coupled receptors up to 1998, and there are over 100 subfamilies classified according to the sequence homology, ligand structure and receptor funcions (beginning of the article of Ji et al.).

Appellant argues that the paper of Yan et al. cites only one example, two isoforms of the anhidrotic ectodermal dysplasia (EDA) gene, where a two amino acid change conforms one isoform (EDA-A1) into the second isoform (EDA-A2) and does not suggest a high level of uncertainty in assigning function based on sequence, and thus does not support the lack of utility. Specifically, Appellant argues that the different receptors bound by the two isofroms of ectodysplasin are related and that EDA-A2 receptor was correctly identified as a member of the tumor necrosis factor receptor superfamily based upon solely on sequence similarity.

This has been fully considered but is not deemed to be persuasive for the following reasons. First, the paper of Yan et al., while citing only one example, clearly demonstrates that the unpredictability of the functions of proteins solely based upon sequence homology. While the two receptors bound by the two isofroms of

ectodysplasin are related, i.e., belonging to the TNFR superfamily, they clearly have different activities (See, e.g., page 524, column 3) and are distinct receptors. Even the title of the paper clearly states that the two receptors bound by the two isoforms are distinct. Secondly, while the EDA-A2 receptor was initially identified as a member of the TNFR superfamily solely based on sequence similarity, as applicants argued, the biological functions of the receptor were not identified. In fact, Yan et al. performed undue experimentation as described in the paper to define the ligand and biological activies of the EDA-A2 receptor. As taught by Yan et al., members of the TNFR superfamily are involved in a number of physiological and pathological response by activating a wide variety of intracellular signaling pathways (beginning of page 523). The EDA-A2 receptor (XEDAR) fails to bind many known ligands of the TNFsuperfamily (1st column of page 524). Therefore, even if sequence analysis could assign a given protein to a protein family, the protein does not necessarily possess the same functions of a member of the family. Consequently, the protein does not have a substantial utiltiy because the biological function or activity is not defined and determining such a biological function of the protein would require significant further research, as demonstrated by Yan et al., which is not allowed under 35 U.S.C.§ 101. As is the case here.

At the second paragraph of page 7 of the Brief, Appellant argues that Appellant has provided evidence of record that conclusively established that those skilled in the

art would believe that the claimed nucleic acid sequence encodes a GPCR, specifically GPR97. Accordingly, the present invention has a patentable utility.

Appellant's argument has been fully considered but is not deemed to be persuasive because the key issue at dispute is not a matter of whether the present nucleic acid encodes a GPCR; rather, it is a matter of whether the present nucleic acid encodes a GPCR with defined biological functions; it is a matter of whether the present nucleic acid sequence has a patentable utility. Even the sequence analysis can place a GPCR into the GPCR family; such an assignment does not render a specific biological function and thus a patentable utility to the GPCR, since there is no single well-established utility for the GPCR family due to the great diversity in structures and functions of the GPCR family and the functions of a GPCR has to be determined experimentally, as noted above.

At the second paragraph of page 8 of the Brief, Appellant argues that the PTO itself does not require 100% identity between proteins to establish functional homology, citing Example 10 of the revised Interim Utility Guidelines Training Materials.

Appellant's argument has been fully considered but is not deemed to be persuasive for the following reasons. In Example 10 of the Revised interim Utility Guidelines Training Materials, the claimed nucleic acid sequence has a well established utility because the high sequence homology can place the protein encoded by the claimed nucleic acid sequence in a DNA ligase family, whereas ligases have a well established use in ligating DNA. It is not the case here.

Beginning at the bottom of page 8 of the Brief, Appellant argues that as 60% of the pharmaceutical products currently being marked by the entire industry target G-protein coupled receptors, a preponderance of the evidence clearly weighs in favor of Appellant's assertion that the skilled artisan would readily recognize that the presently described sequences have a specific, credible, and well-established utility, for example in tracking gene expression, particularly using a gene chip. Appellant further argues that such "DNA chips" clearly have utility, as evidenced by hundreds of issued U.S. Patents and industrial success.

This has been fully considered but is not deemed to be persuasive for the following reasons. First, commercial success is not an indication of patentability and the commercial value does not simply render the claimed invention a specific, substantial, and credible utility. This is because many products may be commercially successful due to reasons unrelated to the use of the products such as fads or clever commercial advertising. For example, a pharmaceutical company may wish to purchase a putative GPCR on the chance that it may turn out to be a drug target in the future, even though determining such possibility requires substantial further experimentation. However, such substantial further experiment is not acceptable for patentable utility. In addition, substantial further experiment may have already been done on some of the GPCRs mentioned by Appellant in the Brief and specific functions may have already been known. This is not the case here.

Secondly, the Examiner would like to draw the Board's attention to the definition of the terms "a gene chip" and " a micro array" mentioned in the Brief and in the instant specification by the Appellant. A gene chip is a customized device in biomedicine that allows researchers to detect, simultaneously, the presence and activity patterns of tens of thousands of DNA sequences in pieces of genetic material. A micro array can be used by researchers to describe the genetic malfunction associated with a disease, detect the presence of the disease in a particular patient, calculate a patient's genetic predisposition to that disease or identify the medicines likely to be most effective in treating a particular patient with the disease.

The instant specification merely asserts that expression of the claimed molecules can be detected in human spleen, bone marrow, and adipose, cells (page 2, lines 13-14) and has not established that the claimed nucleic acid sequences are expressed at altered levels or forms in a specific diseased tissue as compared with the corresponding healthy tissue. If the claimed nucleic acid molecules were in a microarray and a compound caused decreased expression of the claimed nucleic acids, what would that mean to the skilled artisan? Is it a potential drug, or would administering the compound be likely to acerbate an unspecified disease? If it had been disclosed that the claimed nucleic acids are expressed at a higher level in a particular diseased tissue as compared with the corresponding healthy tissue, then the skilled artisan would know that a compound that decreased expression of the nucleic acid molecules is a good drug candidate that targets the disease. It is not the case here. In addition, the claimed nucleic acid molecules may very well be expressed at equivalent levels in healthy

tissues. If that were the case, then the compound would not be a good drug candidate. The claimed nucleic acid molecules may also very well be expressed at a lower level in a particular diseased tissue as compared to the corresponding healthy tissue. Then a compound that decreased expression of the claimed polynucleotides would *not* be a good potential drug. Evidence of a differential expression might serve as a basis for use of the claimed nucleic acid molecule as a diagnostic for a disease. However, in the absence of any disclosed relationship between the claimed nucleic acid molecules (or proteins encoded by the nucleic acids) and any diseases or disorders, any information obtained from an expression profile would only serve as the basis for further research on the observation itself. "Congress intended that no patent be granted on a chemical compound whose sole 'utility' consists of its potential role as an object of use-testing." *Brenner v. Manson*, 148 USPQ at 696. Thus, the disclosure does not present a substantial utility that would support the requirement of 35 U.S.C. §101.

Finally, the issued U.S. Patents related to DNA chips merely show that the technology itself is important and useful; they do not show that claimed invention has a patentable utility. There is no doubt that a gene chip (or DNA chips) is a valuable tool in gene expression monitoring and drug discovery. However, the claims are not drawn to the technique, rather to nucleic acid molecules which have not been disclosed as being associated with any particular diseases or conditions by its being expressed at an altered level or form in a specific diseased tissue as compared to the corresponding healthy tissue. Any such nucleic acid molecules could be added to a micro array. The use of the claimed uncharacterized nucleic acid molecules in such studies would have

provided no more valuable information than the use of any other unidentified nucleic acids. Thus, this asserted utility is not specific. Determining the relationship between the claimed nucleic acid molecules and any specific diseases or disorders would require significant further research. Therefore, this asserted utility is also not substantial.

Beginning at the bottom of page 9 of the Brief, Appellant criticizes the statement "how can an artisan use the claimed sequence in a gene chip format without knowing functions of claimed molecules?" and argues that expression profiling does not require a knowledge of the function of the particular nucleic acid on the chip—rather the gene chip indicates which fragments are expressed at greater or less levels in two or more particular tissue types.

This has been fully considered but is not deemed to be persuasive for the following reasons. First, Appellant is mischaracterizing the Examiner's position. A specification can meet the legal requirements of utility and enablement for a nucleic acid as long as the specification discloses a specific and substantial asserted utility or a well-established utility for the claimed nucleic acids. A hypothetical example may serve to clarify. For example, a hypothetical specification discloses that a claimed nucleic acid is expressed in colon cancer and not expressed in healthy colon tissue. The hypothetical specification does not disclose the biological activity of the polypeptide encoded by the nucleic acid. The claimed nucleic acid in the hypothetical example would not be rejected under 35 U.S.C. §§ 101 and 112, first paragraph, as it has a specific and substantial and is enabled as a colon cancer marker.

However, it is not the case here. The instant specification merely asserts that the nucleic acid sequences of the present invention encode putative human G-protein coupled receptors (see Summary of the Invention) and can be detected in human spleen, bone marrow, and adipose, cells (page 2, lines 13-14). There is no disclosure that the claimed nucleic acids are expressed at altered levels or forms in any specific, diseased tissue. It is noted that the instant application was filed December 7, 2000. No evidence has been brought forth during the prosecution history regarding the expression levels in diseased or healthy tissue; no evidence has been brought forth on the biological activities of the proteins encoded by the present nucleic acids. Since the specification fails to discloses nucleic acid molecules as being associated with any particular diseases or conditions by its being expressed at an altered level or form in a specific diseased tissue as compared to the corresponding healthy tissue, as discussed above, what meaningful results could one possibly obtain even one can carry out the assay using a gene chip?

Furthermore, if Appellant intends to arguing that the present nucleic acid sequences can be used in a gene chip to determine their differential expression associated with a certain disease, it is analogous to argue that the claimed nucleic acid sequences lack a patentable utility in its current available form and establishment of the usefulness requires further significant research.

At page 10, 2nd paragraph of the Brief, Appellant argues that persons of skilled in the art, as well as venture capitalists and investors, readily recognize the utility, both

scientific and commercial, of human genomic data and that the usefulness of the claimed nucleic acid molecules is substantial and credible and well established. This has been fully considered but is not deemed to be persuasive because while human genomic data have both scientific and commercial value, neither the commercial success related to human genomic project nor the publications cited by the Appellant shows a patentable utility for the presently claimed nucleic acid sequences.

Beginning at third paragraph of page 10 of the Brief, Appellant argues that the claimed polynucleotide sequences have utility in "determining the genomic structure", "identification of protein coding sequence", and "identification of exon splice junctions" and provide biologically validated empirical data that specifically define that portion of the corresponding genomic locus that actually encodes exon sequence.

This has been fully considered but is not deemed to be persuasive because such a utility is considered a research utility only designed to identify a particular function of the claimed sequences and is not a substantial utility. See, e.g., *Brenner v. Manson*, 383 U.S. 519, 148 USPQ 689 (Sup. Ct. 1966) wherein a research utility was not considered a "substantial utility." While the Examiner agrees with the Appellant on the scientific value of the claimed polynucleotide sequences and on the significance of expressed sequence information in structural analysis of genomic data, such a use of the polynucleotide sequences in gene mapping does not represent a specific and substantial utility. The exhibit and the publication cited by the Appellant merely show

that the significance of expressed sequences in the structural analysis of genomic data; they do not show that the present polynucleotide sequences have a patentable utility.

Beginning at the bottom of page 11 of the Brief, Appellant argue that the requirement for a specific utility should not be confused with a unique utility, which is clearly an improper standard. Appellant argues, citing case law, that the fact that other expressed sequences could be used to track gene expression patterns on a gene chip, or the fact that a small number of other nucleotide sequences could be used for gene mapping to map the protein coding regions in this specific region of chromosome 16, does not mean that the uses of the present sequences are not specific utilities.

Appellant's arguments have been fully considered but are not deemed to be persuasive for the following reasons. First, Appellant is mischaracterizing the examiner's position regarding the requirements for a specific utility. There is no dispute on the case law itself. The issue at dispute is what constitutes a specific utility. A specific utility is a utility specific to the subject matter claimed. This contrasts with a general utility that would be applicable to the broad class of the invention. To satisfy the utility requirement under 35 U.S.C. § 101, a utility does not need to be unique; however, it must be specific. The use of the present nucleic acid in tracking gene expression patterns on a gene chip is not specific, because such a use would be applicable any nucleic acids. Secondly, it is noted that Appellant fails to specifically disclose the use of the present nucleic acid sequences in mapping the protein coding regions (12 coding exons of the gene encoding SEQ ID NO: 43) in chromosome 16 in the specification as

filed. Appellant only starts to make this specific argument in this brief. Furthermore, as noted above and in the final rejection, such uses are all considered research uses only designed to identify a particular function of the claimed molecules and are not a substantial utility. Thus, all asserted uses are not specific and substantial.

It is further noted that the patents on batteries, automobile tires, golf balls, and treatments for a variety of human diseases are issued by the USPTO because the invention in each patent has a specific and substantial utility, not simply because the claimed subject matter is related to batteries, automobile tires, golf balls, or disease treatment. For example, a golf ball has a specific feature that makes the ball fly higher and further away as compared with other golf balls; a compound has a particular property that can be used to treat a specific disease, e.g., prostate cancer. It is not the case here.

Beginning at the top of page 13 of the Brief, Appellant summarizes case law on the utility requirement. Citing case law, Appellant urges that the present claims clearly meet the requirement of 35 U.S.C. §101. The essential disagreement appears to be the interpretation of what constitutes a specific, substantial and credible utility.

Appellant's arguments have been fully considered but are not deemed to be persuasive for the following reasons. First, the statement, "(t)o violate §101 the claimed device must be totally incapable of achieving a useful result." *Brooktree Corp. v. Advanced Micro Devices, Inc.*, 977 F.2d 1555, 1571, 24 USPQ2d 1401 (Fed. Cir. 1992), indicates that a rejection under 35 U.S.C. § 101 *for lack of operability* can be overcome

by a showing of actual use or commercial success. The claimed invention in the instant case is drawn to nucleic acid sequences, not a device; the instant rejection under 35U.S.C. §101 is not directed to inoperativeness of a device, rather to a lack of patentable utility of the claimed nucleic acid sequences; and the instant issue is whether the asserted utilities meet the three-pronged test for a patentable utility.

Secondly, since the specification fails to disclose a specific, substantial utility or a well-established utility, the present claims do not satisfy the utility requirement of 35 U.S.C. §101. Merely citing case laws on the utility requirement does not render a patentable utility for the present invention. While "anything under the sun that is made by man" is patentable, it does not necessarily mean the present invention is patentable. In fact, the present invention is not patentable due to lack of a patentable utility.

Furthermore, while the FDA approval is not a prerequisite for finding a compound useful within the meaning of the patent laws, and the requirement for the utility of the claimed invention is different from the FDA standard for drug approval, 35 U.S.C. §101 does require a specific, substantial, and credible utility, or well-established utility for an invention. Such a utility has to be a "real world " context of use which does not require significant further research. Appellant confuses this requirement with the "further research and development" needed in pharmaceutical composition and drug development. In other words, a patentable utility has to be clearly identified or immediately apparent in the specification, whereas some "further research and development" is permitted in drug development. For example, determining optimal dosages or drug tolerance in human is further research and development, which is

acceptable under 35 USC 101 because it is not significant. On the other hand, determining a specific disease to be treated by a drug constitutes significant further research and development, which is not acceptable under 35 U.S.C. §101.

In the instant case, the specification fails to disclose the biological functions, physiological significance, or any specific and substantial utility of the claimed molecules. Without such information, how can one in the skilled art use the claimed invention in a meaningful manner? See *Brenner v. Manson*, 383 U.S. 519, 148 USPQ 689 (Sup. Ct. 1966), noting that "a patent is not a hunting license. It is not a reward for the search, but compensation for its successful conclusion."

It is further noted that the instant application was filed December 7, 2000. No evidence on the specific biological functions or physiological significance of the molecules of the present invention has ever been brought forth in an appropriate form during the prosecution history. It weighs clearly in favorite of Examiner's position that significant further research or undue experimentation is required to identify such information.

Finally, at page 15 of the Brief, Appellant challenges the legality of the Patent Examination Utility Guidelines and the validity of issued US patents. It is noted that an Examiner has no authority to comment on the legality of the Guidelines and the validity of US Patents.

Appellant concludes this section by urging that the rejection of claims 1-3 and 6-9 under 35 U.S.C. § 101 must be overruled. The Examiner believes that the rejections should be sustained for the reasons set forth above.

B. Are Claims 1-3 and 6-9 Unusable Due to a lack of Patentable Utility?

As Appellant indicates at page 16 of the Brief, a rejection under U.S.C. § 112, first paragraph, may be affirmed on the same basis as a lack of utility rejection under 35 U.S.C. § 101.

Therefore, for reasons set forth above, Appellant's arguments and exhibits have been fully and carefully considered, but are not considered sufficient to rebut the prima facie case of lack of utility.

For the above reasons, it is believed that the rejections should be sustained.

C. Are Claims 1 and 6-9 Enabled?

Claims 1 and 6-9 are not enabled due to lack of a patentable utility under U.S.C. § 101 for the reasons set forth above.

Furthermore, even if the nucleic acid molecule of SEQ ID NO: 43 or encoding the amino acid sequence set forth in SEQ ID NO: 44 were to have a patentable utility, the instant disclosure would not be found to be enabling for the full scope of the claimed invention comprising a genus of at least 22 contiguous nucleotides of SEQ ID NO: 43, as recited in claim 1. Claims 6 and 9 depend from claim 1. Thus, claims 1, 6, and 9 are further rejected for scope enablement.

Beginning at the bottom of page of 16 of the Brief, Appellant criticizes Examiner's position that the instant disclosure would not be found to be enabling for the whole genus because (i) there is no evidence that 22 residues are sufficient to retain the functions of the full length and (ii) even if so, there is no guidance regarding which 22

residues are sufficient. Appellant submits that the Examiner's comment is completely irrelevant and that there is absolutely no requirement that all species of an invention must have all of the exact same properties. Appellant further submits, citing case law, that it is well established that the enablement requirement is met if any use of the invention (or in this case, certain species of the invention) is provided.

Appellant's arguments have been fully considered but are not deemed to be persuasive for the following reasons. First, the scope enablement issue is judged against the well-established Wands factors, as recited in the office action. The key issue here is the breadth of the claims. Claim 1 is drawn to an isolated nucleic acid molecule comprising at least 22 contiguous bases of nucleotide sequence from SEQ ID NO:43. Thus, the claim recites a genus of nucleic acid molecules of any size comprising at least 22 contiguous nucleotides of SEQ ID NO: 43. While some of species of the genus may retain a readily apparent use if such a use were present for the full-length molecule, the instant disclosure would not be found to be enabling for the whole genus because the instant disclosure fails to show (i) which portions of SEQ ID NO: 43 are critical to the activity of the protein of SEQ ID NO: 44; and (ii) what modifications (e.g., substitutions, deletions or additions) one can make to SEQ ID NO: 43 will result in protein mutants with the same functions as the protein of SEQ ID NO: 44.

Secondly, while there is no requirement for all species of a genus to have exactly same properties, the disclosure has to enable an artisan to make and use the genus. Furthermore, Appellant's argument that the enablement requirement is met if any use of the invention (or in this case, certain species of the invention) is provided is incorrect.

To satisfy the enablement requirement, the disclosure must teach how to make and use the invention. Merely providing asserted uses does not satisfy the enablement requirement under 35 U.S.C. § 112, first paragraph. In the instant case, the disclosure must teach an artisan how to make and use the whole genus, not just the full length nucleic acid sequence of SEQ ID NO: 43, which encodes an amino acid sequence of SEQ ID NO: 44 because the majority of the species of the genus do not obviously encode SEQ ID NO: 44. Finally, the final Action clearly stated that if Appellants intend to claim for a genus of nucleic acid molecules as being used for primers or probes, the instant disclosure fails to provide information or sufficient guidance on how to make and use the claimed genus due to the unpredictable nature of nucleic acid hybridisation and the possibility that a claimed nucleic acid molecule may hybridize to a nucleic acid other than the portion of SEQ ID NO: 43. The final action does not state that the specificity of hybridization is required for all uses of the claimed molecules, as Appellant argued.

At the second paragraph of page 17 of the Brief, Appellant argues that significant commercial exploitation of nucleic acid sequences requires no more information than the nucleic acid sequence itself. Applications ranging from gene expression analysis or profiling (to chromosomal mapping are practiced utilizing nucleic acid sequences and techniques that are well-known to those of skill in the art. Appellant further submit that the skilled artisan can clearly make and use the claimed polynucleotides, which is all that is required to meet the enablement requirement under 35 U.S.C.§112, first paragraph.

Appellant's argument has been fully considered but is not deemed to be persuasive because while nucleic acids may be used in the applications as Appellant argued, Appellant fails to specifically address how the disclosure enable one skilled in the art to make and use the whole claimed genus. As noted above, while some of species of the genus may retain a readily apparent use if such a use were present for the full-length molecule, the instant disclosure would not be found to be enabling for the broad genus.

Beginning at the third paragraph of page 17 of the Brief, Appellant argues that there is sufficient knowledge and technical skill in the art for a skilled artisan to be able to make and use the claimed DNA species in a number of different aspects of the invention entirely without further details in a patent specification.

Appellant's argument has been fully considered but is not deemed to be persuasive because while standard molecular biological techniques are routine in the art, the general teachings in the art are not directed to the specific genus of the nucleic acids of the present invention and do not provide sufficient guidance on how to make and use the claimed genus of nucleic acid molecules. One skilled in the art may be able to use, for example, a nucleic acid molecule consisting of 22 contiguous nucleotide of SEQ ID NO:43 as primers or probes in PCR based screening and determining tissue expression patterns. However, an artisan would not be able to use the claimed broad genus to specifically determine, for example, the expression of the claimed nucleic acid in a tissue, due to the unpredictable nature of nucleic acid hybridisation and the

possibility that a claimed nucleic acid molecule may hybridize to a nucleic acid other than the portion of SEQ ID NO: 43. The state of the art is such that determining the specificity of hybridization is empirical by nature and the effect of mismatches is unpredictable, as taught by Wallace et al. (Methods Enzymol. 152:432-443, 1987) and Sambrook et al. (Molecular Cloning, A Laboratory Manual, 2nd Edition, 1989, Cold Spring Harbor Laboratory, Cold Spring Harbor, NY, page 11.47). Thus, neither the specification nor the art provides sufficient teachings on how to make and use the claimed genus.

Beginning at bottom of page 18 of the Brief, Appellant criticizes the Action by stating that the Action seems to contend that the specification provides insufficient guidance regarding the biological functions or activity of certain of the claimed compositions. Appellant submits that such an enablement standard conflicts with established patent law. Appellant further argues that a considerable amount of experimentation may be permissible if such experimentation is routinely practiced in the art.

Appellant's argument has been fully considered but is not deemed to be persuasive for the following reasons. Appellant clearly mischaracterizes Examiner's position. The scope enablement issue is judged against the well-established Wands factors. What is stated in the Action is that without disclosure of the relation of the function to structure of SEQ ID NO: 44, one skilled in the art would not be able to make and use an isolated nucleic acid molecule comprising at least 22 contiguous bases of

SEQ ID NO: 43, which has 1650 nucleotides and encodes a protein with 549 amino acids. Without disclosing portions of SEQ ID NO: 43 which are critical to the activity of the protein of SEQ ID NO: 44, an artisan would have to perform undue experimentation to find out those species that encoding a functional protein. Thus, different from the situations in cases cited by Appellant, an artisan would not be expected to make and use the claimed genus of nucleic acids, which comprises an enormous number of inoperative species, without undue experimentation.

At the middle of page 19 of the Brief, Appellant argues, citing case law, that a specification "need describe the invention only in such detail as to enable a person skilled in the art in the most relevant art to make and use it."

Examiner agrees that a specification needs to describe an invention only in such detail as to enable an artisan to make and use it. However, the instant specification fails to describe the claimed invention in such detail as to enable an artisan to make and use the claimed genus of nucleic acids for the reasons set forth above.

Beginning at the bottom of page 19 of the Brief, Appellant argues that the specification details numerous applications in which claimed nucleotide sequences can be used, for example, to track gene expression using gene chips. Appellant further submits that since public domain nucleotide sequences that have not been associated with any particular biological function, let alone validated as coding sequences, are used everyday in gene chip applications, it defies logic that undue experimentation would be required to use the presently described nucleotide sequences, which have been biologically validated as coding sequences, in the very same gene chip applications.

This has been fully considered but is not deemed to be persuasive because Appellant's argument fails to address the scope enablement rejection, i.e., how to make and use the genus of nucleic acids. As noted above, while some of species of the genus may retain a readily apparent use if such a use were present for the full-length molecule, the specification would not be found to be enabling for the whole genus.

Appellant concludes this section by urging that the rejection of claims 1, 6, and 9 under 35 U.S.C. § 112, first paragraph must be overruled. The Examiner believes that the rejections should be sustained for the reasons set forth above.

D. Do claims 1 and 6-9 lack sufficient Written Description?

The Examiner would like to clarify that claims 1, 6, and 9 are properly rejected under 35 U.S.C. § 112, first paragraph, for description. Claims 6 and 9 depend from claim 1. Claims 7 and 8, as well as claims 2 and 3 are not rejected.

At the middle of page 20 of the Brief, Appellant argues that Final Action admitted that claim 1 in fact does include a distinguishing feature, specifically, that the nucleic acid molecule must include "a stretch of at least 22 consecutive nucleotides of SEQ ID NO: 43." Appellant further submits that this is all required of claim 1 to meet the written description of 35 U.S.C. § 112, first paragraph.

Appellant's arguments have been fully considered but are not deemed to be persuasive because Appellant mischaracterizes the Examiner's position. The Examiner never states that claim 1 includes a distinguishing feature. In fact, the final Action clearly states that the claim is drawn to a genus of nucleic acid molecules comprising at least 22 contiguous nucleotides of SEQ ID NO: 43. Thus, it encompasses virtually any random sequence of any length as long as it has a stretch of at least 22 consecutive nucleotides of EQ ID NO: 43. The claim does not require that the nucleic acid molecules possess any particular biological activity, nor any particular conserved structure, or other disclosed distinguishing feature.

Beginning at the bottom of page 20 of the Brief, Appellant criticizes the Examiners' position by citing a statement from the Advisory Action, and argues that every aspect of this argument fails to take into consideration the proper basis for compliance with the written description requirement under 35 U.S.C. § 112, first paragraph. Specifically, Appellant argues (i) that the Examiner seems to be requiring that the structural limitation "a stretch of at least 22 consecutive nucleotides of EQ ID NO: 43" have a functional basis; (ii) the limitation of "at least 22 consecutive nucleotides of EQ ID NO: 43" does in fact have a particular conserved structure, specifically, each

and every species is conserved within the nucleotide sequence of SEQ ID NO: 43; and (iii) Examiner's position that the limitation of "at least 22 consecutive nucleotides of EQ ID NO: 43" does not include a distinguishing feature directly contradicts the fact that this limitation is completely free of the prior art.

Appellant's arguments have been fully considered but are not deemed to be persuasive for the following reasons. Appellant obviously mischaracterizes the Examiner's position. The Advisory Action clearly points out that a strech of at least 22 consecutive nucleotides of SEQ ID NO: 43 is not a conserved structure and a distinguising feature, because such a limitation does not require that the nucleic acid molecules possess any particular biological activity. SEQ ID NO: 43 consisting of 1650 nucleotides, there are enormous combinations of "at least 22 consecutive nucleotides of SEQ ID NO: 43", which cover different regions of SEQ ID NO: 43. Consequently, the limitation "at least 22 consecutive nucleotides of EQ ID NO: 43" does not define conserved structure. Consequently, there is no definitive function linked to such a limitation "at least 22 consecutive nucleotides of EQ ID NO: 43". Thus, only an isolated nucleic acid molecule comprising SEQ ID NO:43, but not the full breadth of the claim meets the written description provision of 35 U.S.C. §112, first paragraph. Furthermore, rejections of claims under 35 U.S.C. §112, first paragraph and 35 U.S.C. §102/103 are considered separately. Thus, rejection of claim 1 and its dependent claims 6 and 9 under 35 U.S.C. §112, first paragraph, do not necessarily contradicts the fact that the claims are free of the prior art.

Beginning at the second paragraph of page 21 of the brief, Appellant summarizes the description requirement by citing case law. Appellant argues that the nucleic acid sequence of the present invention are distinguished by structural features—a chemical formula, i.e., the sequence itself. The skilled artisan would readily be able to distinguish the claimed nucleic acids from other materials on the basis of the specific structural description provided.

Appellant's arguments have been fully considered but are not deemed to be persuasive for the following reasons. To provide adequate written description and evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of complete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product, or any combination thereof. In this case, the only factor present in the claim is a recitation of partial structure: comprising at least 22 contiguous nucleotides of SEQ ID NO: 43. There is not even identification of any particular portion of the structure that must be conserved. It is further noted that "comprising at least 22 contiguous nucleotides of SEQ ID NO: 43" is only a partial structure of the genus. It is not a chemical formula because a chemical formula would accurately define the composition of a molecule. Accordingly, in the absence of sufficient recitation of distinguishing identifying characteristics, the specification does not provide adequate written description of the claimed genus. Only an isolated nucleic acid molecule comprising

SEQ ID NO:43, but not the full breadth of the claim meets the written description provision of 35 U.S.C. §112, first paragraph.

Appellant concludes this section by urging that the rejection of claims 1, 6, and 9 under 35 U.S.C. § 112, first paragraph must be overruled. The Examiner believes that the rejections should be sustained for the reasons set forth above.

Respectfully submitted,

Ruixiang Li, Ph.D.
November 11, 2003

Conferees
Yvonne Eyler, Ph.D.
SPE, Art Unit 1646

Anthony Caputa, Ph.D.
SPE, Art Unit 1642